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PATENTE ♦ MARKEN

Process for preparing inherently microbicidal polymer surfaces

The invention relates to a process for preparing antimicrobial polymers by polymerization of amino-functionalized monomers and to the use of antimicrobial polymers prepared in this way.

The invention also relates to a process for preparing antimicrobial polymers by graft-polymerizing amino-functionalized monomers on a substrate and to the use of antimicrobial substrates prepared in this way.

It is highly undesirable for bacteria to become established or to spread on the surfaces of pipelines, containers or packaging. Frequently, slime layers form and permit sharp rises in microbial populations, and these can lead to persistent impairment of the quality of water, drinks or foods, and even to spoilage of the product and harm to the health of consumers.

Bacteria must be kept away from all fields of life in which hygiene is important. This affects textiles for direct body contact, especially in the genital area, and for the care of the elderly and sick. Bacteria must also be kept away from surfaces of furniture and instruments in wards, especially in areas for intensive care and neonatal care, in hospitals, especially in areas for medical interventions, and in isolation wards for critical cases of infection, and also in toilets.

A current method of treating equipment, or the surfaces of furniture or textiles, to resist bacteria either when this becomes necessary or else as a precautionary measure, is to use chemicals or solutions of mixtures of these which, as disinfectants, have a fairly broad general antimicrobial action. Chemical agents of this type act nonspecifically and are frequently themselves toxic or irritant, or form degradation products which are hazardous to health. In addition, people frequently exhibit intolerance to these materials once they have become sensitized.

Another method to counteract surface spread of bacteria is to incorporate substances with antimicrobial action into a matrix.

Tert-butylaminoethyl methacrylate is a commercially available monomer in methacrylate chemistry and is used in particular as a hydrophilic constituent in copolymerizations. For example, EP-B 0 290 676 uses various polyacrylates and polymethacrylates as a matrix for immobilizing bactericidal quaternary ammonium compounds.

In another technical sector US-A 4 532 269 discloses a terpolymer of butyl methacrylate, tributyltin methacrylate and tert-butylaminoethyl methacrylate. This polymer is used as an antimicrobial paint for ships: the hydrophilic tert-butylaminoethyl methacrylate promotes gradual erosion of the polymer, thus liberating the highly toxic tributyltin methacrylate as antimicrobial agent.

In these applications the copolymer prepared using aminomethacrylates is merely a matrix or carrier substance for added microbicidal agents which can diffuse or migrate out of the carrier substance. Sooner or later polymers of this type lose their effectiveness once the "minimal inhibitory concentration" (MIC) is no longer achieved on the surface.

European Patent Applications 0 862 858 and 0 862 859 have disclosed that homo- and copolymers of tert-butylaminoethyl methacrylate with a methacrylate having a secondary amino function have inherent microbicidal properties. To avoid undesirable resistance phenomena in the microbes, particularly bearing in mind the development of resistance by bacteria known from antibiotics research, systems developed in the future will need to continue to be based on novel compositions and have improved effectiveness.

The object of the present invention is therefore to develop novel polymers having antimicrobial action. These, where appropriate in the form of a coating, should prevent the establishment and spread of bacteria on surfaces.

Surprisingly, it has now been found that polymerizing aliphatically unsaturated monomers which have been at least singly functionalized by means of a secondary amino group gives polymers with a long-lasting microbicidal surface which is not attacked by solvents or by physical stresses and which does not exhibit migration. This makes it unnecessary to use other biocides.

The present invention provides a process for preparing antimicrobial polymers, which comprises polymerizing aliphatically unsaturated monomers which have been at least singly functionalized by means of a secondary amino group.

The aliphatically unsaturated monomers used in the process according to the invention and at least singly functionalized by means of a secondary amino group may have a hydrocarbon radical of up to 50 carbon atoms, preferably up to 30 carbon atoms, particularly preferably up to 22 carbon atoms. The substituents of the amino group may be aliphatic or vinylic hydrocarbon radicals, such as methyl, ethyl, propyl or acrylic radicals, or cyclic hydrocarbon radicals, such as substituted or unsubstituted phenyl or cyclohexyl radicals having up to 25 carbon atoms. The amino group may also have substitution by keto or aldehyde groups, such as acryloyl or oxo groups.

To achieve a sufficient rate of polymerization, the monomers used according to the invention should have a molar mass of less than 900, preferably less than 550 g/mol.

A particular embodiment of the present invention uses aliphatic unsaturated monomers functionalized by means of a secondary amino group and having the general formula

$$R^1NR^2H$$

where R^1 is a branched, unbranched or cyclic, saturated or unsaturated hydrocarbon radical having up to 50 carbon atoms which

may have substitution by O atoms, N atoms or S atoms, and

R^2 is a branched, unbranched or cyclic, saturated or unsaturated hydrocarbon radical having up to 25 carbon atoms, which may have substitution by O atoms, N atoms or S atoms.

Suitable monomer building blocks, besides the secondary-amino-functionalized acrylates and methacrylates described in European Applications 0 862 858 and 0 862 859, are any aliphatically unsaturated monomers which have at least one secondary amino function, for example ethyl 3-phenylmethylamino-2-butenoate, ethyl 3-ethylamino-2-butenoate, ethyl 3-methylamino-2-butenoate, 3-methylamino-1-phenyl-2-propen-1-one, N-4-methylamino-1-anthraquinoyl(2-methyl)acrylamide, N-9,10-dihydro-4-(4-methylphenylamino)-9,10-dioxo-1-anthraquinyl-2-methylpropenamide, propyl 2-hydroxy-3-(3-triethoxysilylpropylamino)-2-propenoate, 1-(1-methylethyl-amino)-3-(2-(2-propenyl)phenoxy)-2-propanol hydrochloride, ethyl 3-phenylamino-3-methyl-2-butenoate, 1-(1-methylethylamino)-3-(2-(2-propenyloxy)phenoxy)-2-propanol hydrochloride, methyl 2-acrylamido-2-methoxyacetate, methyl 2-acetamidoacrylate, N-tert-butylacrylamide, 2-hydroxy-N-2-propenylbenzamide and N-methyl-2-propenamide.

The novel process can also be carried out by polymerizing the monomers at least singly functionalized by means of a secondary amino group on a substrate. This gives a physisorbed coating made from the antimicrobial copolymer on the substrate.

Suitable substrate materials are especially any of the polymeric plastics, such as polyurethanes, polyamides, polyesters and polyethers, polyether block amides, polystyrene, polyvinyl chloride, polycarbonates, polyorganosiloxanes, polyolefins, polysulfones, polyisoprene, polychloroprene, polytetrafluoroethylene (PTFE) or corresponding copolymers or blends, or also naturally occurring or synthetic rubbers, with or without radiation-sensitive groups. The novel process may also be used on surfaces of objects

made from metal, from glass or from wood and surface-coated or otherwise coated with plastic.

In another embodiment of the present invention the antimicrobial polymers may be obtained by graft-polymerizing a substrate with an aliphatically unsaturated monomer at least singly functionalized by means of a secondary amino group. The grafting of the substrate allows covalent linking of the antimicrobial polymer to the substrate. Substrates which may be used are any polymeric material, such as the plastics mentioned above.

Prior to the graft polymerization, the surfaces of the substrate may be activated by a variety of methods. Any standard method for activating polymer surfaces may be used here, for example the substrate may be activated prior to the graft polymerization by UV radiation, plasma treatment, corona treatment, flame treatment, ozonization, electrical discharge or γ-radiation. The surfaces are usefully freed in advance in a known manner from oils, fats or other contamination, using a solvent.

The substrate may be activated using UV radiation in the wavelength range from 170 to 400 nm, preferably from 170 to 250 nm. An example of a suitable radiation source is a Noblelight UV excimer apparatus from HERAEUS, Hanau, Germany. However, mercury vapor lamps are also suitable for substrate activation as long as they emit substantial proportions of radiation in the abovementioned ranges. The exposure time is generally from 0.1 seconds to 20 minutes, preferably from 1 second to 10 minutes.

The activation of the standard polymers with UV radiation may moreover also use a photosensitizer. For this, the photosensitizer, such as benzophenone, is applied to the substrate surface and irradiated. A mercury vapor lamp may again be used here, with exposure times of from 0.1 seconds to 20 minutes, preferably from 1 second to 10 minutes.

According to the invention, the activation may also be by plasma treatment using an RF or microwave plasma (Hexagon, Technics Plasma, 85551

Kirchheim, Germany) in air, nitrogen or argon atmospheres. The exposures times are generally from 2 seconds to 30 minutes, preferably from 5 seconds to 10 minutes. The energy supplied in the case of laboratory devices is from 100 to 500 W, preferably from 200 to 300 W.

Corona devices (SOFTAL, Hamburg, Germany) may also be used for activation. The exposure times in this case are generally from 1 to 10 minutes, preferably from 1 to 60 seconds.

Activation by electrical discharge, electron beam or γ-radiation (e.g. from a cobalt 60 source), and also ozonization, allow short exposure times, generally from 0.1 to 60 seconds.

Substrate surfaces may also be activated by flame treatment. Suitable devices, in particular those with a barrier flame front, can readily be constructed or, for example, purchased from ARCOTEC, 71297 Mönsheim, Germany. They may be operated using hydrocarbons or hydrogen as combustion gas. In all cases it is necessary to avoid damage to the substrate by overheating, and this can readily be ensured if the side of the substrate facing away from the flame treatment side is in intimate contact with a cooled metal surface. Activation by flame treatment is therefore restricted to relatively thin, sheet-like substrates. The exposure times are generally from 0.1 seconds to 1 minute, preferably from 0.5 to 2 seconds. The flames are exclusively nonluminous, and the distances between the substrate surfaces and the outer side of the flame front are from 0.2 to 5 cm, preferably from 0.5 to 2 cm.

The substrate surfaces activated in this way are coated by known methods, such as dipping, spraying or spreading, where appropriate in solution. Solvents which have proven useful are water and water/ethanol mixtures, but other solvents may also be used as long as they are sufficiently capable of dissolving the monomers and give good wetting of the substrate surfaces. Examples of other solvents are ethanol, methanol, methyl ethyl ketone, diethyl ether, dioxane, hexane, heptane, benzene, toluene, chloroform, dichloromethane, tetrahydrofuran and acetonitrile. Solutions with monomer

contents of from 1 to 10% by weight, for example about 5% by weight, have proven successful in practice and generally give, in a single pass, coherent coatings which cover the substrate surface and have thicknesses which can be more then 0.1 μm.

The graft copolymerization of the monomers applied to the activated surfaces may usefully be initiated by radiation in the short-wave segment of the visible range or in the long-wave segment of the UV range of electromagnetic radiation. For example, the radiation from a UV excimer of wavelengths from 250 to 500 nm, preferably from 290 to 320 nm, is very suitable. Mercury vapor lamps are also suitable here as long as they have substantial proportions of radiation in the abovementioned ranges. The exposure times are generally from 10 seconds to 30 minutes, preferably from 2 to 15 minutes.

Graft copolymerization can also be achieved by a process described in European Patent Application 0 872 512 and based on a graft polymerization of monomer molecules and initiator molecules incorporated by swelling.

The process of the invention uses the abovementioned monomers to prepare homopolymers. There is no requirement for the use of other monomers.

Even without grafting to a substrate surface, the antimicrobial polymers prepared according to the novel process made from aliphatically unsaturated monomers which have been at least singly functionalized by means of a secondary amino group show microbicidal or antimicrobial behavior.

If the novel process is used directly on the substrate surface without grafting, conventional free-radical initiators may be used. Examples of initiators which

may be used are azonitriles, alkyl peroxides, hydroperoxides, acyl peroxides, peroxoketones, peresters, peroxocarbonates, peroxodisulfate, persulfate and any of the usual photoinitiators, such as acetophenones, α-hydroxyketones, dimethylketals and benzophenone. The polymerization may also be initiated thermally or, as already stated, by electromagnetic radiation, such as UV light or γ-radiation.

Use of the modified polymer substrates

The present invention also provides the use of the antimicrobial polymers prepared according to the invention to produce antimicrobially active products, and the products per se which are produced in this way. The products may comprise polymer substrates modified according to the invention or consist of these. Products of this type are preferably based on polyamides, polyurethanes, polyether block amides, polyesteramides or -imides, PVC, polyolefins, silicones, polysiloxanes, polymethacrylate or polyterephthalates surface-modified using polymers prepared according to the invention.

Examples of antimicrobially active products of this type are in particular machine parts for processing food and drink, components in air-conditioning systems, roofing, items for bathroom and toilet use, kitchen items, components of sanitary equipment, components of cages or houses for animals, recreational products for children, components of water systems, packaging for food or drink, operator units (touch panels) of devices, and contact lenses.

The present invention also provides the use, to produce hygiene products or items in medical technology, of the polymer substrates whose surfaces have been modified using the antimicrobial polymers prepared according to the invention. That which has been said above concerning preferred materials applies correspondingly. Examples of hygiene products of this type are toothbrushes, toilet seats, combs and packaging materials. The term hygiene items also includes objects which may come into contact with a large number of people, such as telephone handsets, stair rails, door handles, window catches, and grab straps and grab handles in public conveyances. Examples

of items in medical technology are catheters, tubing, protective or backing films and also surgical instruments.

The polymers, copolymers or graft polymers prepared by the novel process may be used anywhere where importance is placed on surfaces with release properties or surfaces which are very free from bacteria, i.e. microbicidal. Examples of application of microbicidal polymers or graft polymers prepared according to the novel process are in particular surface coatings, protective paints and other coatings in the following sectors:

Marine: Boat hulls, docks, buoys, drilling platforms, ballast water tanks

Construction: Roofing, basements, walls, facades, greenhouses, sun protection, garden fencing, wood protection

- Sanitary: Public conveniences, bathrooms, shower curtains, toilet items, swimming pool, sauna, jointing, sealing compounds

Requisites for daily life: Machines, kitchen, kitchen items, sponge pads, recreational products for children, packaging for food or drink, milk processing, drinking water systems, cosmetics

Machine parts: Air-conditioning systems, ion exchangers, process water, solar-powered units, heat exchangers, bioreactors, membranes

Medical technology: Contact lenses, diapers, membranes, implants

Consumer articles: Automobile seats, clothing (socks, sport clothing), hospital equipment, door handles, telephone handsets, public conveyances, animal cages, cash registers, wall-to-wall carpets, wallpapers.

The following examples are given in order to describe the present invention in greater detail, but are not intended to limit its scope as set out in the claims.

Example 1:

A nylon-12 film is exposed for 2 minutes at a pressure of 1 mbar to radiation at 172 nm from a Heraeus excimer source. The film activated in this way is placed into an irradiator under inert gas and held in place. In a countercurrent of inert gas the film is then covered with 20 ml of a mixture of 3 g of methyl 2-acrylamido-2-methoxyacetate (Aldrich) and 97 g of methanol. The radiation chamber is sealed and placed at a distance of 10 cm from a Heraeus excimer unit emitting at 308 nm. Irradiation is begun and continued for 15 minutes. The film is then removed and rinsed with 30 ml of methanol, then dried in vacuo for 12 hours at 50°C. The film is then extracted in water 5 times for 6 hours at 30°C, then dried at 50°C for 12 hours.

The reverse side of the film is then treated in the same way, finally giving a polyamide film coated on both sides with grafted polymer.

Example 1a:

A coated piece of film from Example 1 (5 by 4 cm) is shaken in 30 ml of a test microbial suspension of Staphylococcus aureus. After a contact time of 15 minutes, 1 ml of the test suspension is removed and the number of microbes in the test mixture is determined. After expiry of this time no Staphylococcus aureus microbes are now detectable.

Example 1b:

A coated piece of film from Example 1 (5 by 4 cm) is shaken in 30 ml of a test microbial suspension of Pseudomonas aeruginosa. After a contact time of 60 minutes, 1 ml of the test suspension is removed and the number of microbes in the test mixture is determined. After expiry of this time the number of microbes has fallen from 10^7 to 10^4.

Example 2:

A nylon-12 film is exposed for 2 minutes at a pressure of 1 mbar to radiation at 172 nm from a Heraeus excimer source. The film activated in this way is placed into an irradiator under inert gas and held in place. In a countercurrent of inert gas the film is then covered with 20 ml of a mixture of 3 g of methyl 2-acetamidoacrylate (Aldrich) and 97 g of methanol. The radiation chamber

is sealed and placed at a distance of 10 cm from a Heraeus excimer unit emitting at 308 nm. Irradiation is begun and continued for 15 minutes. The film is then removed and rinsed with 30 ml of methanol, then dried in vacuo for 12 hours at 50°C. The film is then extracted in water 5 times for 6 hours at 30°C, then dried at 50°C for 12 hours.

The reverse side of the film is then treated in the same way, finally giving a polyamide film coated on both sides with grafted polymer.

Example 2a:

A coated piece of film from Example 2 (5 by 4 cm) is shaken in 30 ml of a test microbial suspension of Staphylococcus aureus. After a contact time of 15 minutes, 1 ml of the test suspension is removed and the number of microbes in the test mixture is determined. After expiry of this time the number of microbes has fallen from 10^7 to 10^4.

Example 2b:

A coated piece of film from Example 2 (5 by 4 cm) is shaken in 30 ml of a test microbial suspension of Pseudomonas aeruginosa. After a contact time of 60 minutes, 1 ml of the test suspension is removed and the number of microbes in the test mixture is determined. After expiry of this time the number of microbes has fallen from 10^7 to 10^4.

Example 3:

A nylon-12 film is exposed for 2 minutes at a pressure of 1 mbar to radiation at 172 nm from a Heraeus excimer source. The film activated in this way is placed into an irradiator under inert gas and held in place. In a countercurrent of inert gas the film is then covered with 20 ml of a mixture of 3 g of N-tert-butylacrylamide (Aldrich) and 97 g of methanol. The radiation chamber is sealed and placed at a distance of 10 cm from a Heraeus excimer unit emitting at 308 nm. Irradiation is begun and continued for 15 minutes. The film is then removed and rinsed with 30 ml of methanol, then dried in vacuo for 12 hours at 50°C. The film is then extracted in water 5 times for 6 hours at 30°C, then dried at 50°C for 12 hours.

The reverse side of the film is then treated in the same way, finally giving a

polyamide film coated on both sides with grafted polymer.

Example 3a:

A coated piece of film from Example 3 (5 by 4 cm) is shaken in 30 ml of a test microbial suspension of Staphylococcus aureus. After a contact time of 15 minutes, 1 ml of the test suspension is removed and the number of microbes in the test mixture is determined. After expiry of this time no Staphylococcus aureus microbes are now detectable.

Example 3b:

A coated piece of film from Example 3 (5 by 4 cm) is shaken in 30 ml of a test microbial suspension of Pseudomonas aeruginosa. After a contact time of 60 minutes, 1 ml of the test suspension is removed and the number of microbes in the test mixture is determined. After expiry of this time the number of microbes has fallen from 10^7 to 10^4.

Example 4:

A nylon-12 film is exposed for 2 minutes at a pressure of 1 mbar to radiation at 172 nm from a Heraeus excimer source. The film activated in this way is placed into an irradiator under inert gas and held in place. In a countercurrent of inert gas the film is then covered with 20 ml of a mixture of 3 g of methyl 2-acrylamido-2-methoxyacetate (Aldrich), 2 g of methyl methacrylate (Aldrich) and 95 g of methanol. The radiation chamber is sealed and placed at a distance of 10 cm from a Heraeus excimer unit emitting at 308 nm. Irradiation is begun and continued for 15 minutes. The film is then removed and rinsed with 30 ml of methanol, then dried in vacuo for 12 hours at 50°C. The film is then extracted in water 5 times for 6 hours at 30°C, then dried at 50°C for 12 hours.

The reverse side of the film is then treated in the same way, finally giving a polyamide film coated on both sides with grafted polymer.

Example 4a:

A coated piece of film from Example 4 (5 by 4 cm) is shaken in 30 ml of a test microbial suspension of Staphylococcus aureus. After a contact time of

15 minutes, 1 ml of the test suspension is removed and the number of microbes in the test mixture is determined. After expiry of this time no Staphylococcus aureus microbes are now detectable.

Example 4b:

A coated piece of film from Example 4 (5 by 4 cm) is shaken in 30 ml of a test microbial suspension of Pseudomonas aeruginosa. After a contact time of 60 minutes, 1 ml of the test suspension is removed and the number of microbes in the test mixture is determined. After expiry of this time the number of microbes has fallen from 10^7 to 10^4.

Example 5:

A nylon-12 film is exposed for 2 minutes at a pressure of 1 mbar to radiation at 172 nm from a Heraeus excimer source. The film activated in this way is placed into an irradiator under inert gas and held in place. In a countercurrent of inert gas the film is then covered with 20 ml of a mixture of 3 g of methyl 2-acetamidoacrylate (Aldrich), 2 g of methyl methacrylate (Aldrich) and 95 g of methanol. The radiation chamber is sealed and placed at a distance of 10 cm from a Heraeus excimer unit emitting at 308 nm. Irradiation is begun and continued for 15 minutes. The film is then removed and rinsed with 30 ml of methanol, then dried in vacuo for 12 hours at 50°C. The film is then extracted in water 5 times for 6 hours at 30°C, then dried at 50°C for 12 hours.

The reverse side of the film is then treated in the same way, finally giving a polyamide film coated on both sides with grafted polymer.

Example 5a:

A coated piece of film from Example 5 (5 by 4 cm) is shaken in 30 ml of a test microbial suspension of Staphylococcus aureus. After a contact time of 15 minutes, 1 ml of the test suspension is removed and the number of microbes in the test mixture is determined. After expiry of this time no Staphylococcus aureus microbes are now detectable.

Example 5b:

A coated piece of film from Example 5 (5 by 4 cm) is shaken in 30 ml of a test microbial suspension of Pseudomonas aeruginosa. After a contact time of 60 minutes, 1 ml of the test suspension is removed and the number of microbes in the test mixture is determined. After expiry of this time the number of microbes has fallen from 10^7 to 10^4.

In addition to the microbicidal action described above with respect to cells of Pseudomonas aeruginosa and Staphylococcus aureus, all of the specimens also exhibited microbicidal action with respect to cells of Klebsiella pneumoniae, Escherichia coli, Rhizopus oryzae, Candida tropicalis and Tetrahymena pyrifomis.